



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> : <b>A61K 9/51, 9/16</b>		<b>A3</b>	(11) International Publication Number: <b>WO 96/20698</b>
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(21) International Application Number: PCT/US96/00476 (22) International Filing Date: 4 January 1996 (04.01.96) (30) Priority Data: 08/369,541      5 January 1995 (05.01.95)      US 08/389,893      16 February 1995 (16.02.95)      US (60) Parent Application or Grant (63) Related by Continuation US      08/839,893 (CON) Filed on      16 February 1995 (16.02.95) (71) Applicant (for all designated States except US): THE BOARD OF REGENTS acting for and on behalf of THE UNIVERSITY OF MICHIGAN [US/US]; c/o Technology Management Office, Wolverine Tower, Room 2071, 3003 South State Street, Ann Arbor, MI 48109-1280 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): LEVY, Robert, J. [US/US]; 2241 Belmont, Ann Arbor, MI 48104 (US). LABHASETWAR, Vinod, D. [IN/US]; 4844 Washtenaw, Ann Arbor, MI 48108 (US). SONG, Cunxian, S. [CN/US];		5014 Kresge II, Box 0576, Ann Arbor, MI 48109-0576 (US). (74) Agents: ROHM, Benita, J. et al.; Miller, Canfield, Paddock and Stone, plc, Suite 2500, 150 W. Jefferson Avenue, Detroit, MI 48226 (US). (81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AZ, BY, KZ, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments. (88) Date of publication of the international search report: 22 January 1998 (22.01.98)	
(54) Title: SURFACE-MODIFIED NANOPARTICLES AND METHOD OF MAKING AND USING SAME			
(57) Abstract			
<p>Biodegradable controlled release nanoparticles as sustained release bioactive agent delivery vehicles include surface modifying agents to target binding of the nanoparticles to tissues or cells of living systems, to enhance nanoparticle sustained release properties, and to protect nanoparticle-incorporated bioactive agents. Unique methods of making small (10 nm to 15 nm, and preferably 20 nm to 35 nm) nanoparticles having a narrow size distribution which can be surface-modified after the nanoparticles are formed is described. Techniques for modifying the surface include a lyophilization technique to produce a physically adsorbed coating and epoxy-derivatization to functionalize the surface of the nanoparticles to covalently bind molecules of interest. The nanoparticles may also comprise hydroxy-terminated or epoxide-terminated and/or activated multiblock copolymers, having hydrophobic segments which may be polycaprolactone and hydrophilic segments. The nanoparticles are useful for local intravascular administration of smooth muscle inhibitors and antithrombogenic agents as part of interventional cardiac or vascular catheterization such as a balloon angioplasty procedure; direct application to tissues and/or cells for gene therapy, such as the delivery of osteotropic genes or gene segments into bone progenitor cells; or oral administration in an enteric capsule for delivery of protein/peptide based vaccines.</p>			
ATTORNEY DOCKET NUMBER: 10271-021-999 SERIAL NUMBER: 09/724,531 REFERENCE: BB			

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# INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 96/00476

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 6 A61K9/51 A61K9/16

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K C08J C08G

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JOURNAL OF CONTROLLED RELEASE, vol. 25, no. 1/02, 27 May 1993, AMSTERDAM (NL), pages 89-98, XP000361370 T. NIWA ET AL.: "PREPARATIONS OF BIODEGRADABLE NANOSPHERES OF WATER-SOLUBLE AND INSOLUBLE DRUGS WITH D.L.-LACTIDE/GLYCOLIDE COPOLYMER BY A NOVEL SPONTANEOUS EMULSIFICATION SOLVENT DIFFUSION METHOD, AND THE DRUG RELEASE BEHAVIOR" see the whole document --- -/--	1,4-7, 12,14, 17,18, 39,40, 45-48, 68-71, 75,76

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

4 September 1997

Date of mailing of the international search report

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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 96/00476

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SCIENCE, vol. 263, 18 March 1994, WASHINGTON (US), pages 1600-1603, XP002013571 R. GREF ET AL.: "BIODEGRADABLE LONG-CIRCULATING POLYMERIC NANOSPHERES" see the whole document ---	1
X	JOURNAL OF CONTROLLED RELEASE, vol. 25, no. 1/02, 27 May 1993, AMSTERDAM (NL), pages 145-153, XP000361376 P.D. SCHOLLES ET AL: "THE PREPARATION OF SUB-200NM POLY(LACTIDE-CO-GLYCOLIDE) MICROSPHERES FOR SITE-SPECIFIC DRUG DELIVERY" see the whole document ---	2
A	see the whole document ---	45,53, 68,81
X	WO 93 00076 A (MINNESOTA MINING & MFG) 7 January 1993 see page 8 - page 9 see example 1 ---	10,11
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X	JOURNAL OF MICROENCAPSULATION, vol. 5, no. 2, 1988, LONDON (GB), pages 115-127, XP002013572 J. KREUTER: "POSSIBILITIES OF USING NANOPARTICLES AS CARRIERS FOR DRUGS AND VACCINES" see page 118 ---	19
X	EP 0 529 711 A (LABORATORIOS CUSI, S.A.) 3 March 1993  see the whole document ---	1,2,4-8, 12,29, 31,34
X	WO 91 15193 A (RHONE-POULENC RORER S.A.) 17 October 1991  see the whole document ---	1-8,12, 29, 31-33,35
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# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 96/00476

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 95 22963 A (MEDINOVA MEDICAL CONSULTING GMBH) 31 August 1995  see page 6 - page 27 ---	1-8, 10-18, 21-23, 26,29, 35-37, 39,40, 54,55, 63,82, 83,97,98
X	WO 94 18955 A (ALZA CORPORATION) 1 September 1994  see page 4, line 5 - page 6, line 6 see page 8, line 12 - line 16 see page 17; example 3 see claims 1-8,13-21 ---	1-5,12, 17-19, 21, 29-32, 39,40, 54,55, 82,83
A	WO 92 17167 A (BIOTECH AUSTRALIA PTY. LTD.) 15 October 1992 see the whole document ---	9
A	JOURNAL OF CONTROLLED RELEASE, vol. 3, no. 1, January 1986, AMSTERDAM (NL), pages 15-23, XP002033952 S. J. DOUGLAS ET AL.: "poly(butyl 2-cyanoacrylate) nanoparticles with differing surface charges" see the whole document ---	11,30
X	EP 0 407 580 A (TERUMO CORP) 16 January 1991 see claims 1,4,7,9 ---	104,105, 108,114
X	EP 0 336 964 A (TERUMO CORP) 18 October 1989 see claims 1,2,6-8 ---	104,105, 108,114
A	EP 0 335 972 A (TERUMO CORP) 11 October 1989 see claims 1,22,23,32 ---	104
A	WO 90 10034 A (BASF CORP) 7 September 1990 see claim 1 -----	115

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 96/ 00476

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
Remark: Although claims 141-148, 152-154, 156-158 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effect of the composition.
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. Claims: 1-8, 10-28, 39-44, 88-96, 141-148, 152-154, 156-158(all partly); 45-53, 68-81
2. Claims: 1-8, 10-28, 39-44, 141-148, 152-154, 156-158(all partly); 9, 29-38, 54-67  
82-87, 97-103, 149-151, 155
3. Claims: 104-114
4. Claims: 115-140

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 96/00476

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Information on patent family members

International Application No

PCT/US 96/00476

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